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COMPARING THREE MOTOR THRESHOLD ESTIMATION METHODS USING SIMULATION AND NAVIGATED TRANSCRANIAL MAGNETIC STIMULATION

Thesis submitted for examination for the degree of Master of Science in
Technology

Espoo September 7, 2009

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Title: Comparing Three Motor Threshold Estimation Methods Using
Simulation and Navigated Transcranial Magnetic Stimulation

Date: September 7, 2009 Language: English Number of pages: 10+50

Faculty: Faculty of Electronics, Communications and Automation

Professorship: Computational Engineering (Cognitive Technology) Code: S-114

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This thesis discusses different methods to estimate motor threshold. Motor threshold is an important measure of cortical excitability, and it is applied, for instance, in transcranial magnetic stimulation therapy for treatment of depression. However, a standard way to estimate this value is yet to be formed.

To proceed towards a standard, it is useful to compare the performance of several methods. This study is the first, in which different estimation methods are compared against each other using not only simulation but navigated transcranial magnetic stimulation as well.

The objective of the study conducted was to find the best estimation method to implement as a computerized tool by comparing three estimation methods against each other. The best method was selected using the following characteristics: accuracy, precision, number of stimuli used, and the estimation time.

The estimation methods to be compared were chosen such that they could be implemented as a computer program easily. The methods chosen were: Awiszus' Maximum Likelihood method, Mills-Nithi method, and a new variant of the maximum likelihood approach.

A method, which can be implemented as a computer program is less exposed to the operator's own opinion. Thus, motor threshold estimates become more comparable.

The study was conducted in two parts. The first part was a simulation and the second part a navigated TMS study. Five subjects attended the TMS study. There were two operators present at each session. All of the subjects and operators were familiar with TMS.

Based on these results, the main differences arose from the number of stimuli used and the length of the estimation. The estimates themselves differed only little. Therefore, a standard should be chosen such that it is easy to apply in any situation and is understandable by the operator regardless of experience level.

Keywords: motor threshold, Transcranial Magnetic Stimulation, simulation, estimation method, navigated stimulation, comparison study

Tekijä: Hanna Kumpula

Työn nimi: Kolmen Motorisen Kynnyksen Estimointimenetelmän Vertailu
Simulaation ja Navigoidun Transkraniaalisen
Magneettistimulaation Avulla

Päivämäärä: 07.09.2009

Kieli: Englanti

Sivumäärä: 10+50

Tiedekunta: Elektroniikan, tietoliikenteen ja automaation tiedekunta

Professuuri: Laskennallinen tekniikka (Kognitiivinen teknologia) Koodi: S-114

Valvoja: Professori Mikko Sams

Ohjaaja: FT Ilkka Autio

Tämä diplomityö käsittelee motorisen kynnyksen estimointimenetelmien vertailua. Motorinen kynnys on tärkeä kortikaalisen eksitoituvuuden mitta, jota käytetään muun muassa masennushoidon yhteydessä, kun hoitomuotona on transkraniaalinen magneettistimulaatio -terapia. Mitä estimointiin ei kuitenkaan ole valikoitunut yhtä standardoitua tapaa.

Standardin saavuttamiseksi on vertailtava useiden eri menetelmien suoriutuvuutta. Tehty tutkimus on ensimmäinen laatuaan, jossa estimointimenetelmiä verrataan paitsi simulaation, myös navigoidun transkraniaalisen simulaation avulla. Tutkimuksen tavoitteena oli valita kolmesta estimointimenetelmästä paras sovelukseksi implementoitava vertailemalla menetelmiä toisiinsa. Parhauden kriteerejä olivat menetelmän tarkkuuden lisäksi käytettävien impulssien lukumäärä sekä estimointiin käytetty aika.

Vertailtavat estimointimenetelmät valittiin siten, että ne määrittelivät selkeän algoritmin, jolloin niiden implementointi sovellukseksi olisi suoraviivaista. Tällainen menetelmä olisi suojassa operaattorin omilta päätelmiltä, jolloin estimaattien keskinäinen vertailu paranee. Menetelmiksi valikoituivat Awiszuksen suurimman uskottavuuden menetelmä, Mills-Nithin menetelmä, sekä uusi versio suurimman uskottavuuden menetelmästä.

Vertailututkimuksen ensimmäisessä vaiheessa menetelmien suoritumista vertailtiin simuloimalla. Toisessa vaiheessa tehtiin koehenkilömittauksia viidelle koehenkilölle. Operaattoreita oli läsnä kaksi jokaisessa mittaustilanteessa. Transkraniaalinen magneettistimulaatio oli kaikille tuttua entuudestaan.

Saatujen tulosten perusteella suurimmat eroavuudet liittyivät käytettyjen impulssien lukumäärään ja estimointiin käytettyyn aikaan. Itse estimaattiarvojen välillä oli vain pieniä eroja. Näin ollen, estimointimenetelmän standardi tulisi valita siten, että sitä on helppo soveltaa missä käyttötilanteessa hyvänsä eikä operaattorin harjaantuneisuuden taso ole esteenä menetelmän ymmärtämiselle.

Avainsanat: motorinen kynnys, Transkraniaalinen magneettistimulaatio, simulointi, estimointimenetelmä, navigoitu stimulointi, vertailututkimus

Acknowledgements

This master's thesis was funded by Nexstim Ltd. It has truly been an unforgettable journey in the world of medical technology.

I wish to thank my supervisor, Professor Mikko Sams, for showing interest in my thesis. In addition, I am grateful to my instructor Ilkka Autio for the valuable advice he gave on the subject of scientific writing and for pointing out logical flaws.

I am also indebted to Mika Inki for his knowledge of mathematical methods; and Mervi Könönen and her team at KUH for conducting the TMS studies.

To all my wonderful colleagues at Nexstim: thank you for teaching me how TMS works, giving me insight on medical procedures, and for your support.

Finally, I thank my husband and little son for being patient and constantly reminding me of life and what is really important. I also thank my husband for challenging my writing in a way no one else dared.

Espoo, September 7, 2009

Hanna Kumpula

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Symbols and Abbreviations

Symbols

E_{ion}	equilibrium potential of <i>ion</i>
V_m	membrane resting potential
R	universal gas constant
T	absolute temperature in degrees Kelvin
z	valence of the ion
F	Faraday constant
p_{ion}	permeability for the ion
$[ion]_o, [ion]_i$	ion concentration outside and inside the cell, respectively
\mathbf{E}	electric field intensity
\mathbf{B}	magnetic flux density
t	time
\mathbf{H}	magnetic field intensity
\mathbf{J}	current density
\mathbf{D}	electric flux density
σ	conductivity of the material
$p(m, t, s)$	probability for success
m	stimulus intensity
t	threshold
s	threshold spread
$L(t, s)$	log-likelihood function
ms	intensities eliciting a response
mf	intensities incapable of eliciting a response
t	maximum likelihood threshold estimate
s	maximum likelihood threshold spread estimate
v	random variable
tt	true threshold

Abbreviations

3D	Three-dimensional
AC	Alternating Current
AML	Awiszus Maximum Likelihood
aMT	active Motor Threshold
APB	Abductor Pollicis Brevis (thumb muscle)
AT	Approximate Threshold
BBB	Blood-brain Barrier
CNS	Central nervous system
EMG	Electromyography
IFCN	International Federation of Clinical Neurophysiology
KUH	Kuopio University Hospital
LT	Lower Threshold
MEP	Motor Evoked Potential
MN	Mills-Nithi
MR	Magnetic Resonance
MS	Multiple Sclerosis
MT	Motor Threshold
NBS	Navigated Brain Stimulation
NML	New variant of Maximum Likelihood
PEST	Parameter Estimation by Sequential Testing
PNS	Peripheral nervous system
PSO	Percentage of Stimulator Output
rMT	resting Motor Threshold
rTMS	repetitive Transcranial Magnetic Stimulation
TMS	Transcranial Magnetic Stimulation
UT	Upper Threshold

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1 Introduction

The medical field benefits from precise treatment protocols and agreed methods. Furthermore, used measures in patient-records must be repeatable. One such procedure is the transcranial magnetic stimulation (TMS) therapy for treatment of depression, in which the dosage is proportioned to the patient's motor threshold (MT) of the right thumb muscle [1]. TMS is a noninvasive method to stimulate the brain using magnetic fields. MT is a value currently used as a measure of cortical excitability.

As a biological system, the human body is constantly changing state, which means that stimulating twice with the same intensity may result in different outcomes. Therefore, MT cannot be a single value but rather has a statistical nature. It is defined as the stimulator intensity with which 50% of stimuli elicit a response on the target muscle. Hence, MT is estimated rather than measured.

Many different estimation methods for MT have been developed. However, not all suggested methods include a precise algorithm on how to proceed. They seem to, at least partially, rely on operator's experience. In addition, some estimate MT with the target muscle relaxed (resting MT, rMT), whereas others think it is better to keep the target muscle under constant tension (active MT, aMT). Furthermore, there exists no agreed way for determining a response: some use an electromyography (EMG) recording device and classify resulting motor evoked potentials (MEP) against some predefined amplitude threshold, while others define a response as a visible twitch of the target muscle. Even the used equipment has an effect as the induced electric fields on the cortex generated by different stimulators are not identical. Thus, two MT values may not be comparable.

To proceed towards a standard, it is useful to compare the performance of several methods. This has, indeed, been done in previous studies. Used methods have included TMS studies and one study has used simulation.

However, nearly every study has modified at least one of the estimation methods included in the comparison in some way. Furthermore, there exists no study, where the original methods have been compared using both simulation and TMS. Additionally, such a comparison has not been carried out using navigated TMS. This study, then, was the first to compare different estimation methods using not only simulation but navigated TMS as well.

The objective of this study was to find the best estimation method to implement as a computerized tool by comparing three estimation methods against each other. The best method was selected using the following characteristics: accuracy, precision, number of stimuli used, and the estimation time. Of the last two, smallest values were considered best. These have been in focus in the previous studies as well.

Focusing on computerization affected the selection of comparable methods. An estimation method was qualified, if it defined an explicit starting intensity; took input as response information; and gave the next stimulation intensity as output. The three

methods selected were: Mills-Nithi (MN), maximum likelihood approach introduced by one Awiszus (AML), and a new variant of maximum likelihood approach (NML).

The pursuit of the standard way justifies the selected focus, since an explicitly defined algorithm prevents the operator to employing his own opinions in the estimation process. Thus, MT estimates by different operators become more comparable. Furthermore, the operator needs not to think about the protocol on hand, but is able to fully concentrate on stimulating. Thus, the estimation processes themselves are more reliably compared.

This study was limited to estimate rMT of the right hand thumb muscle - *Abductor Pollicis Brevis* (APB). Responses were defined using an EMG device and setting the amplitude threshold as 50 μV .

Structure of Thesis

Chapter 2 Describes the structure of human brain and explains how the TMS-evoked signal propagates through the body to move the thumb.

Chapter 3 Introduces TMS. Reviews the history of TMS development, explains the underlying physical phenomena, and presents a modern-day TMS device.

Chapter 4 Introduces the concept of MT in detail. Explains the definition and usage as well as describes different estimation methods.

Chapter 5 Describes the methods and analysis techniques used in this study.

Chapter 6 Presents results from the study.

Chapter 7 Discusses this study and the results in a more general manner.

Chapter 8 Contains conclusions drawn from the results presented in Chapter 6.

2 How to Move a Muscle

This chapter aims to clarify how the TMS-evoked signal travels through the human body and causes the thumb muscle to twitch. The thumb is chosen as an example, since in the study the MT is estimated for it. The chapter begins by introducing the basic building blocks of the nervous system and explains how the signals and signaling networks are formed. Then, the structure of the human brain is presented and the starting point of the *pyramidal tract* (i.e., the information highway for muscle controlling signals) is located. Finally, the route from the brain to the thumb muscle is followed.

2.1 Basics Structures and Signaling

In 1790's Luigi Galvani found that electric current caused a dead frog's legs to move [18]. Since then it has been known that also the human body is controlled by electricity. The incoming signals (for example, light through eyes, pressure through skin, or sound through ears) are transformed into electrical form, transferred to and processed in the brain. Once a decision has been made on how to react, the outgoing signals are also delivered in electrical form.

Thus, the whole human body can be thought to be an information processing system. The smallest processors of this system are the cells, which have their own specific tasks and functions. This thesis concentrates on cell types in the central and peripheral nervous systems (CNS and PNS, respectively).

This section explains the basics of the signaling in the nervous system. First, the two main classes of cells, neurons and glial cells, are introduced. Then, the mechanisms connected with signaling are described.

Neurons

Neurons, as all cells, come in various shapes and sizes and are specialized to execute the task assigned to them. Some neurons receive signals directly from outside the human body through receptors and deliver them to be analyzed in the brain, some are specialized in delivering signals to muscles ordering them to move, and some merely act as delivering channels or processing units in between. Structure of a typical neuron is presented in Figure 1. Furthermore, Table 1 introduces different classes of neurons. In addition, there are neurons which do not have either *dendrites* or *axons* at all [33].

Typically dendrites receive the incoming signals and deliver them to the cell body (*soma*) where they are processed. The outgoing information leaves the cell through the axon which begins from a structure called *axon hillock* and ends in *axon terminals*, where the electrical information is transformed into chemical via the release of neurotransmitters into the *synapse* (i.e., the gap between two neurons). However, some neurons are capable of delivering or receiving signals in electrical form.

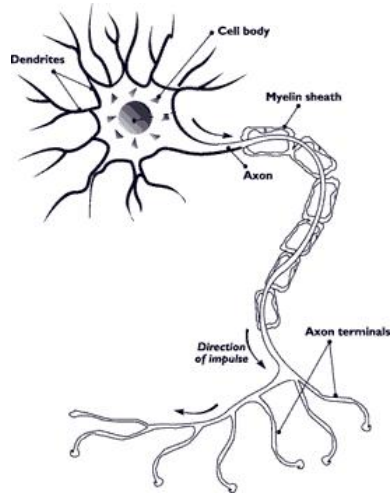


Figure 1: Basic structure of a typical neuron. Direction of the signal is from dendrites to axon terminals. Figure from [35].

Table 1: Neuron classes and their typical tasks. Figures modified from [19, p. 30]

Type	Description	Typical task	
Unipolar	One branch leaves from the body. It may further branch to form <i>axon terminals</i> and <i>dendrites</i> .	Typically found in invertebrates.	
Bipolar	One <i>axon</i> and one dendrite branch off from the body.	Typically located in sensory areas, where they are one of the first neurons to receive the incoming messages. (Visual, auditory, and sense of smell.)	
Pseudounipolar	Like bipolar neurons, but with axon and dendrite merged near the body.	Take part in transporting the signals from somatosensory areas. (Skin, muscles, and joints.)	
Multipolar	Multiple dendrites attached to the body but only one axon leaves.	Typically take part in processing motor and sensory information.	

Through synapses, every neuron is connected to at least one other neuron. The neuron sending information is referred to as *presynaptic*, whereas the receiving neuron is called *postsynaptic*. Synapses are classified by their location on the receiving neuron: *axo-axonal* are located in the axon, *axo-somatic* in the cell body, and *axodendritic* in the dendrites. With the multiple dendrites and axon terminals the neuron not only receives signals from many other neurons (information *convergence*) but delivers its own signal to multiple neurons (information *divergence*) as well. Neuron axons combine together to form nerves, which deliver a large amount of signals (i.e., information) related to some subject (e.g., visual information or orders to move a muscle) between two areas of the body. [19, 23, 25, 33]

Glial Cells


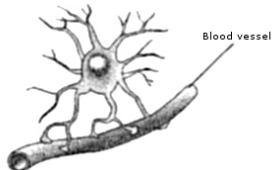
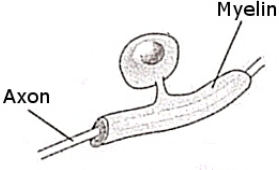
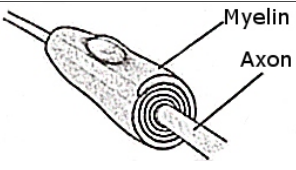
There are about a tenfold of glial cells in the brain compared to neurons. The structural difference between glial cells and neurons is the lack of axons. Table 2 introduces the main classes of glial cells found in CNS and PNS, as well as their main functions. Oligodendrocytes and Schwann cells are the most important when it comes to moving the muscles, since the myelin speeds up the signal conduction in axons. [33]

Signaling

Neurons are "made of" *neuronal membrane*, which consists of a bilayer of lipid molecules. Its function is to keep the surrounding *tissue fluid* and the neuron's internal fluid (*cytoplasm*) from mixing. Within the lipids there are also protein molecules acting, for example, as *ion channels*, *pumps*, and *receptor molecules*. Ion channels may be passive, being always open to certain ions, or activated by some mechanism (an activating ion, voltage, or even membrane stretching). Pumps are involved in active transaction processes and create ionic concentration gradients across the membrane. Na-K -pump is the most important of these. Receptor molecules exist in the synapses. They remain closed until a right kind of neurotransmitter is received. [19, 25, 33]

Tissue fluid has a high concentration of sodium ions (Na^+) whereas the cytoplasm has a high concentration of potassium ions (K^+). There are also chloride ions (Cl^-) present in both liquids. Using the *Nernst equation* (Eq. 1) the *equilibrium potentials* for sodium and potassium can be calculated ($E_{Na^+} \approx +60 \text{ mV}$ and $E_{K^+} \approx -75 \text{ mV}$). In addition, the *membrane resting potential* can be calculated using the *Goldman equation* (Eq. 2) ($V_m \approx -70 \text{ mV}$).

Table 2: Main classes of glial cells in the nervous system. [19,25,33] (Figures modified from [19, p. 30])

Location	Class	Main functions	
CNS	Microglia	Act as the sanitary system. They fill damaged areas and also function as <i>phagocytes</i> (cells that are capable of removing damaged cells or other unwanted material [42]).	
	Astrocytes	Encapsulate synapses, form a barrier between spinal fluid and nerve tissue, and form the blood-brain barrier (BBB).	
	Oligodendrocytes	Form myelin around neuron axons in the CNS. One oligodendrocyte is capable of forming myelin around multiple axons.	
PNS	Schwann cells	Form myelin around neuron axons in the PNS.	

$$E_{ion} = \frac{RT}{zF} \ln \frac{[ion]_o}{[ion]_i} \quad (1)$$

,where ion refers to the ion under examination
 R is the universal gas constant
 T is the absolute temperature in degrees Kelvin
 z is the *valence* of the ion
 F is the Faraday constant
 $[]_o$ and $[]_i$ are the ion concentrations outside and inside the cell, respectively

$$V_m = \frac{RT}{F} \ln \frac{p_{K^+} [K^+]_o + p_{Na^+} [Na^+]_o + p_{Cl^+} [Cl^+]_i}{p_{K^+} [K^+]_i + p_{Na^+} [Na^+]_i + p_{Cl^+} [Cl^+]_o} \quad (2)$$

,where R is the universal gas constant
 T is the absolute temperature in degrees Kelvin
 F is the Faraday constant
 p is the permeability for the ion
 $[]_o$ and $[]_i$ are the ion concentrations outside and inside the cell, respectively
[19, 25, 33]

The equilibrium potential is the voltage difference between the inside and outside of the membrane when there is no movement of the ions through it. That is, if the potassium ions were allowed to move freely across the membrane, then after equalization of the K^+ ion concentrations, the measured voltage would be approximately -75 mV . The membrane resting potential, on the other hand, is the measured potential level when the neuron is at rest. As one can see, when a neuron is resting, it is actually keeping itself off balance. Without this disequilibrium, however, the signaling would not be possible at all. [19]

When neurotransmitters carry the signal-dependent chemicals across the synapse they activate some of the receptor molecules in the postsynaptic neuron membrane. Depending on the type of the neurotransmitter, this has either *excitatory* or *inhibitory* effect. Excitatory means, that resulting ion flow depolarizes the membrane (potential increases). In contrast, inhibitory means that the membrane is hyperpolarized (potential decreases). [19]

If the membrane near the axon hillock depolarizes enough to cross a threshold of approximately -55 mV , the neuron is caused to fire and an *action potential* is released. The action potential is a short pulse during which the membrane first depolarizes reaching a peak in the range of $+30 - +40 \text{ mV}$ and then repolarizes back to the resting state. Figure 2 shows a schematic picture of the action potential. In detail, the depolarization causes the voltage-sensitive ion channels for sodium to open and sodium ions flow into the neuron trying to equalize the concentration differences. This causes the potential to rapidly rise toward the equilibrium potential of sodium. After a while (around 1 ms), the voltage-sensitive ion channels for potassium open, potassium ions flow out, and at the same time the sodium channels are closing. The outflow of the potassium ions cancels the depolarization of the

membrane and turns it into hyperpolarization, which continues until the equilibrium potential of potassium is reached. This means that the membrane is hyperpolarized. Na-K -pumps then activate and restore the resting potential by pumping sodium out and potassium in. [19]

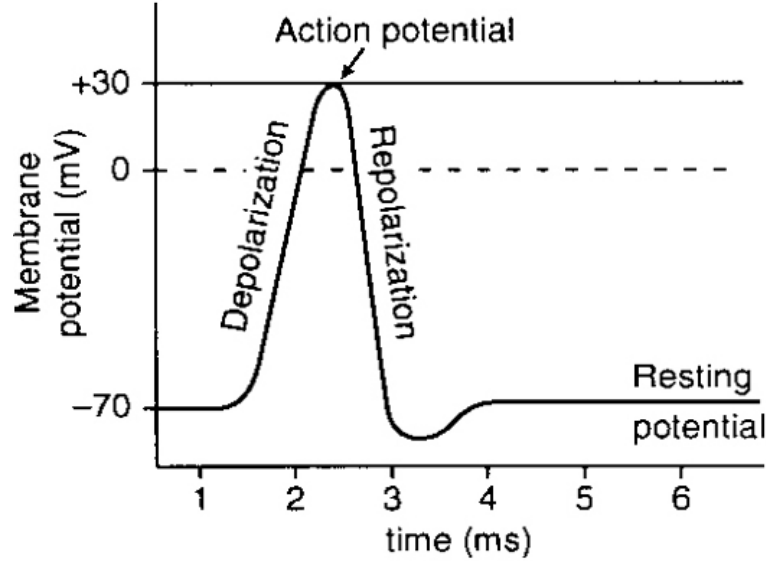


Figure 2: Schematic picture of an action potential [2].

The action potential is the key for signaling. It is always formed once the depolarization crosses the threshold and has the same amplitude and duration every time. This is called the "all-or-none" -principle. Even though the amplitude of the action potential remains unchanged, the neuron will fire more often when the intensity of the signals grows. Thus, signaling in the network seems to be based on frequency modulation. [25]

Every action potential is followed by a *refractory period* during which the neuron cannot fire. It begins when the sodium channels close as they cannot open for a short period of time. In addition, while the Na-K -pumps are restoring the resting potential, firing is also more difficult. Furthermore, neurons have a tendency of firing at random - i.e., without an incoming signal. [19,33]

The action potential travels along the axon in the following manner: opening of the sodium channels and the following sodium inflow causes more of them to open ahead. The sodium inflow is followed by the opening of the potassium channels and potassium outflow. Thus it seems that the action potential travels unchanged when in reality it is generated in real time at each point on the axon. Figure 3 shows the propagation of the action potential in an instant of time. [19,33]

One needs to note, that if the depolarization does not cross the threshold level, the channels won't open and the potential merely fades and might not reach the axon terminals at all. [19,33]

The mechanism described above holds for unmyelinated axons. The action potential

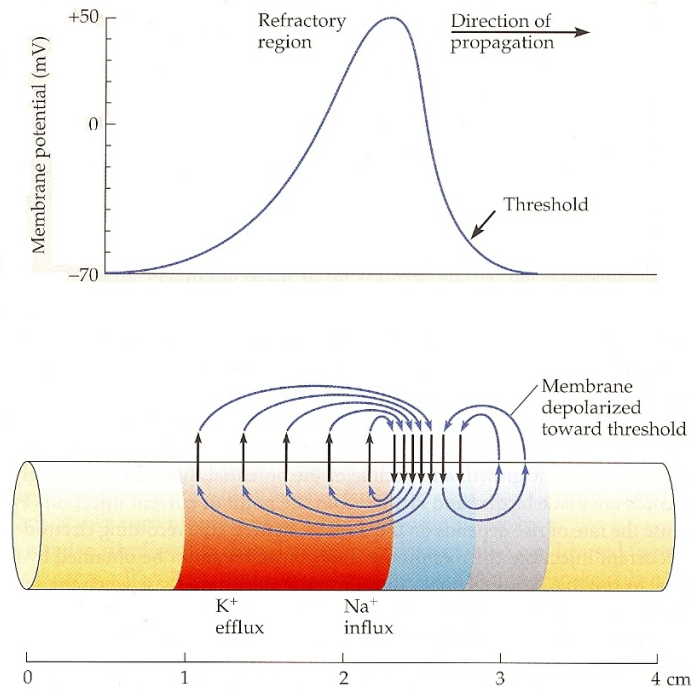


Figure 3: Action potential in an instant of time [33, p. 122].

travels along the axon with a velocity of 2 m/s . Myelin enables the action potential to travel faster (even over 100 m/s) by a conduction method called the *saltatory conduction*. A glial cell (oligodendrocyte or Schwann cell) produces myelin sheaths (Figure 1) around an axon by wrapping itself around it. Myelin insulates the axon, such that there are small gaps, called the *nodes of Ranvier*, between myelin sheaths. When action potential travels along the myelinated axon, the inflow of the sodium ions activate the sodium channels at the next node of Ranvier. The same happens with the potassium ions and the action potential seems to jump from one node of Ranvier to the next. Figure 4 illustrates this. [19]

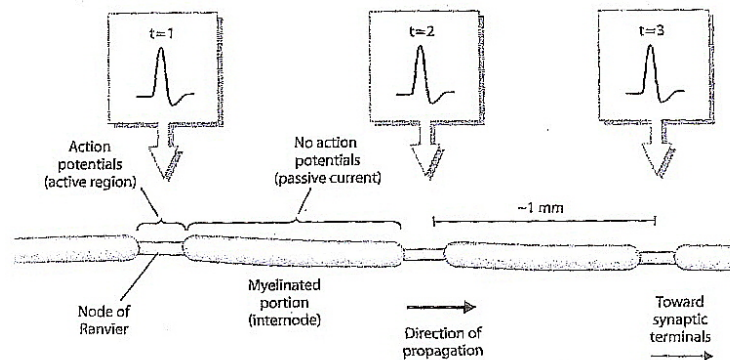


Figure 4: Saltatory conduction [19, p. 49].

Especially motor neurons with their long axons are myelinated to enable fast signaling and thus moving.

2.2 Brain and the Nervous System

The CNS forms the information processing center for the signals commanding our bodies. It consists of the brain (*encephalon*) and the spinal cord (*medulla spinalis*) and is surrounded by bones: the brain rests inside the skull and the spinal cord is protected by the spine (*vertebral column*). The brain consists of *cerebrum*, *cerebellum*, and *brain stem* (*truncus cerebri*), but in this thesis we will concentrate on the cerebrum, although, it must be mentioned that the cerebellum is also greatly involved in motoric processes. The cerebrum is divided into two hemispheres which are further divided into lobes. The right hemisphere is in control of the left side of the body and vice versa. Hemispheres have almost identical functions, although some differences have been discovered. For example right-handed people seem to have the language-related processing areas in the left hemisphere. [44] The spinal cord acts as the main channel for signals to and from the brain. [19, 25, 44]

Both the brain and the spinal cord are made of neuronal tissue. A cross-section of the brain or the spinal cord shows two colored layers of this tissue. These are referred to as white and gray matter. White matter is formed by myelinated neuron axons and thus represents the "wiring". Gray matter covers the outer part of the brain and is formed by the cell bodies. In contrast, in the spinal cord the white matter surrounds the gray matter. In the cerebrum the layer of gray matter is referred to as the *cerebral cortex* [44]. It is only a few millimeters thick, but contains six different layers which tells us that there is a lot of processing involved. [19, 44]

As previously mentioned, the hemispheres are divided into lobes of which there are four (Figure 5). The most frontal is the *frontal lobe*, behind it the *parietal lobe* and below is the *temporal lobe*. The back most lobe is called the *occipital lobe*. Furthermore, the cerebral cortex is organized in terms of processing different kinds of information. Somatic sensory area (*somatosensory cortex*) is located in the parietal lobe and processes the somatic information. Motor control areas (*motor cortex*) are located in the frontal lobe and processes the motor information. Between motor and somatosensory cortices is *central fissure*, which is an important physiological landmark for locating the motor cortex. [44]

The somatosensory and motor cortices are organized such that they each contain a map of the body. The maps in somatosensory and motor cortices are usually referred to as *sensory homunculus* and *motor homunculus* and they are presented in Figure 6. As is seen, the maps are distorted. The larger the processing area of a specific body part is, the more neurons there are associated with it. In addition, some differences can be seen between the two homunculi.

Recent studies have, however, shown that motor movements are not as simple as simply activating a few neurons and seeing the corresponding muscles moving. Firstly, all movements are planned and activation in the motor cortex can be detected be-

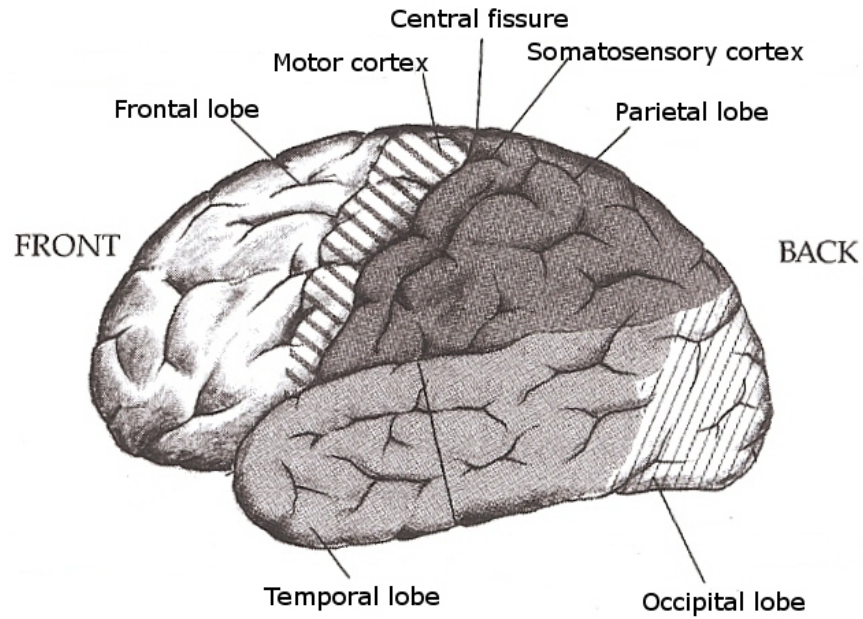


Figure 5: Brain lobes, motor and somatosensory cortices, and central fissure. (Modified from [44, p. 24].)

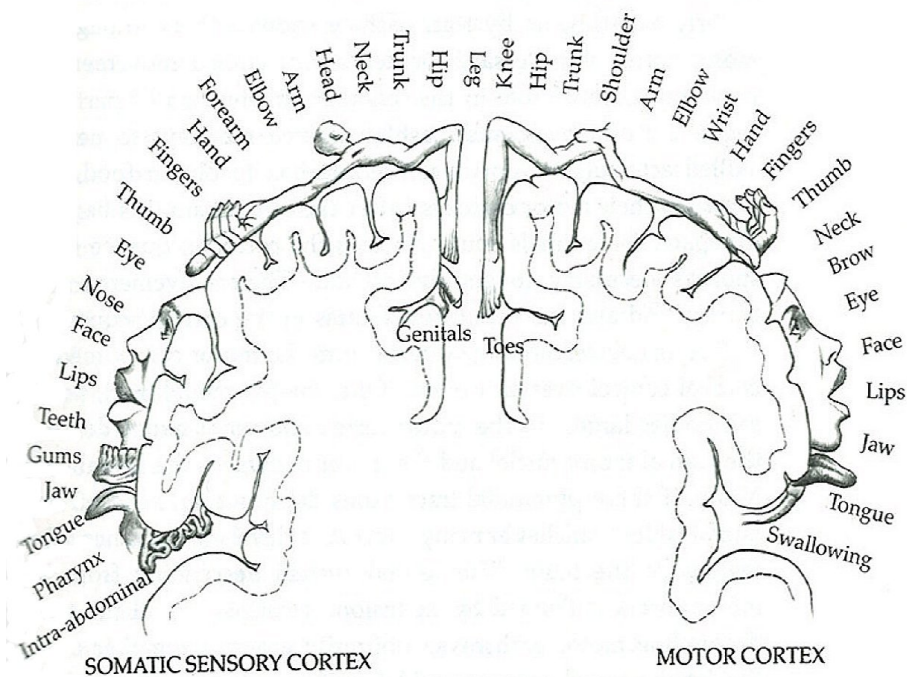


Figure 6: Representations of the muscles in the sensory and motor cortices. Figure from [44]

fore movement. Thus, when one even thinks of moving a thumb muscle, the neurons activate but the thumb does not actually move. In addition, the discovery of *mirror neurons* has proved that simply seeing someone else move a thumb activates the "thumb-moving neurons" of the observer. Today, it is also known, that the motor cortex has a key role in learning motor sequences and that motor cortex neurons need to be activated before one is able to perceive himself moving. [14]

Motor signals leave the motor cortex through the pyramidal tract. This tract starts from the pyramidal cells (hence the name) on motor cortex and continues through the brain stem to the spinal cord. Only a small fraction of the leaving signals continue past the brain stem due to a strong feedback between the motor and sensory areas. This feedback enables the learning of new movements. [25]

MAJOR MOTOR PATHWAYS

Tracts descending to the spinal cord

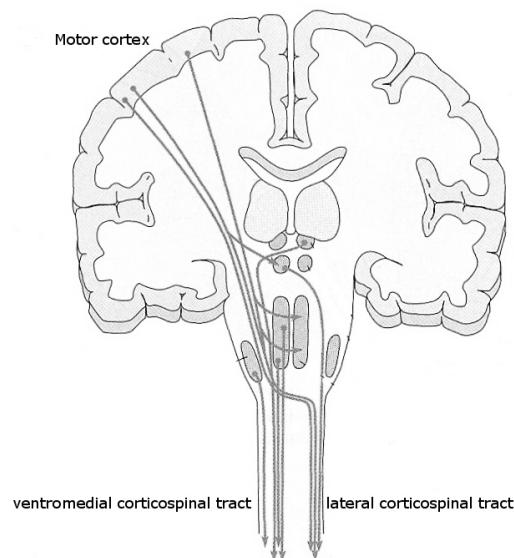


Figure 7: Major motor pathways. Figure from [33, App. C-8]

There are, actually, two pyramidal tracts, which deliver different types of signals at different times and for different purposes. For example, during a reach-and-grasp movement, signals concerning the reach-part flow through *lateral corticospinal tract* to the contralateral side, whereas signals concerning the grasp-part flow through *ventromedial corticospinal tract*. [14, 16]

From the spinal cord, the signals move on to the PNS. To reach the thumb, they branch from the spinal cord at the *brachial plexus*, which is a nerve formation on the side of the neck. From there they follow *median nerve*, whose branch controls the thumb muscle - i.e., APB. Figure 8 shows the nerves involved on route to the APB muscle. [24]

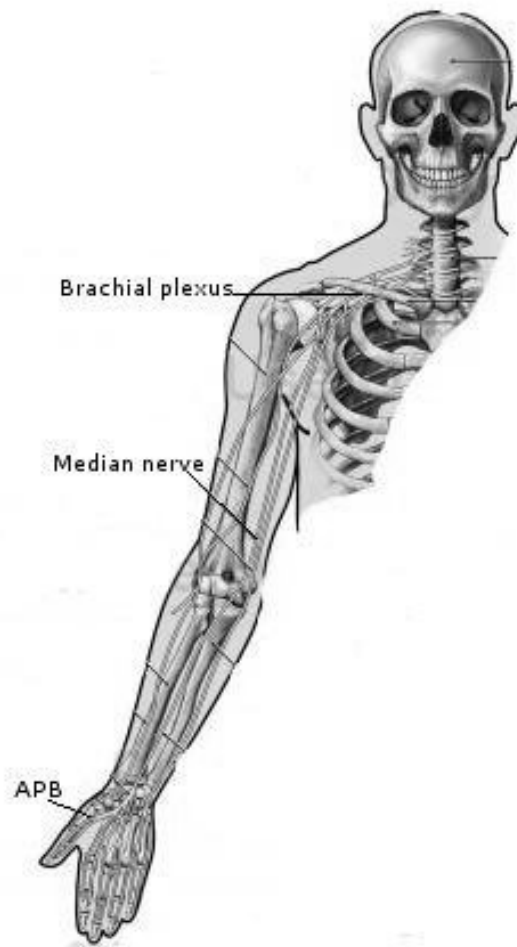


Figure 8: Signal's route from spinal cord to thumb muscle. Figure modified from [3]

Figure 9 presents different sensory pathways for incoming sensory information. Signals come through different pathways depending on their purpose. [33]

2.3 Summary

Two main classes of cells exist in the nervous system. Neurons handle the signal processing and glial cells have supportive functions. Neurons form a signaling network through synapses and deliver the signal with the help of neurotransmitters. These cause the membrane of the postsynaptic neuron to either depolarize (excitatory signal) or hyperpolarize (inhibitory signal). If the membrane depolarizes enough, an action potential is released towards other neurons.

The most important glial cells are the oligodendrocytes and the Schwann cells, which produce myelin around the neuron axons. Myelin insulates the axons and enables the fast propagation of signals.

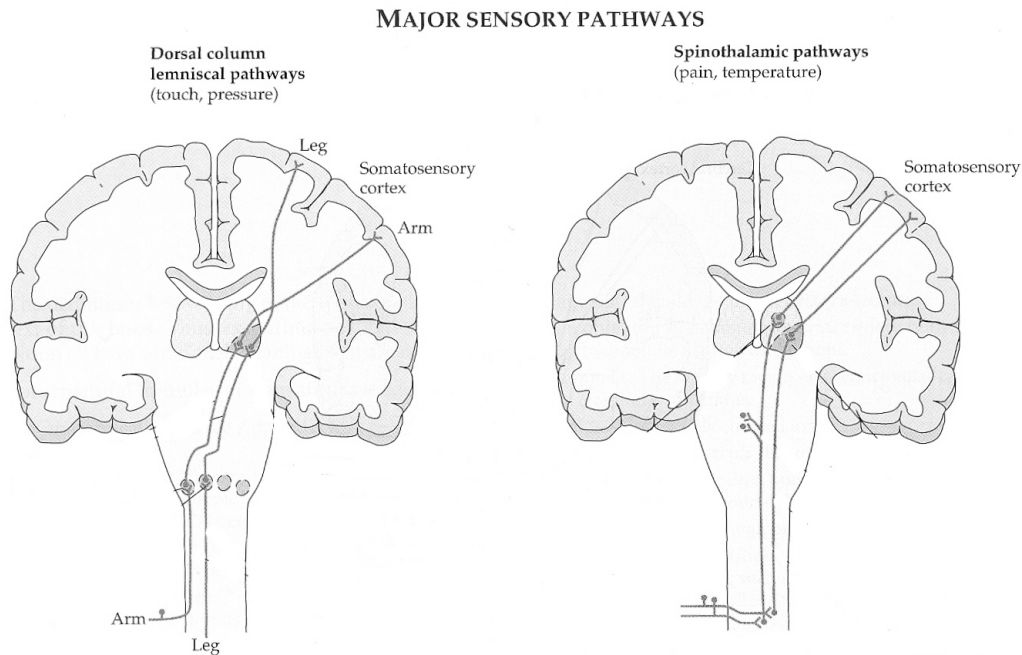


Figure 9: Major sensory pathways. Figure from [33, App. C-7]

CNS consists of brain and the spinal cord. The brain is formed by two hemispheres, which are further divided into four lobes. The outer part of the brain is referred to as cerebral cortex, which is divided into processing areas. Motor and sensory cortices are the processing areas for motor and sensory information. They are located in the junction of frontal and parietal lobe. Different areas on the body are represented in the motor and sensory cortices and arranged such that they form a map of the body.

Moving requires complex procedures. The neurons, which activate when the thumb actually moves, also activate when a person thinks of moving the thumb or simply observes someone else move.

The signals ordering the thumb to move travel through the pyramidal tract. It starts from the motor cortex to the spinal cord, branches from the neck and follows median nerve to the thumb.

3 Transcranial Magnetic Stimulation

This chapter explains how magnetic fields can be used to move a person's thumb. First, the history of TMS is reviewed. Then, the physical laws enabling this phenomenon are explained. Finally, the equipment and usage of a modern TMS device are introduced.

3.1 History of Transcranial Magnetic Stimulation

According to several authors, the first person to report the effects of magnetic field on human body was Arsenne d'Arsonval in 1896. He reported that subjects experienced visual sensations, flickering lights called *phosphenes* or *magnetophosphenes*, when exposed to a time-varying magnetic field. [9, 11, 21]

In 1910 Silvanus Thompson conducted an experiment with the magnetic fields and also discovered phosphenes apparently unaware of d'Arsonval's experiment. Thompson had, however, learned from the lectures of Lord Kelvin that Lord Lindsay had tried experimenting with static magnetic fields before and reached a conclusion that magnetic fields have no effect on humans. Figure 10 shows Thompson's setup. [4, 43, 45, 46]



Figure 10: Silvanus Thompson's experiment setup. Figure from [7].

Magnusson and Stevens confirmed Thompson's discovery in 1911. Additionally, they tried to stimulate cat's exposed sciatic nerve (i.e., a large nerve on leg) with no significant success: only slight muscle twitching was observed. [28] In 1947, Barlow et al. compared electrical stimulation to magnetic fields in phosphene production

and noticed that both methods elicit them. In addition, they tried to magnetically stimulate the occipital region without success. [11]

In 1959 Kolin et al. confirmed the phenomenon of phosphenes. They concluded that these phenomena had to be caused by eddy currents induced in the retinal cells by the time-varying magnetic field and went on to magnetically stimulate an exposed frog's nerve in two different setups, both of which resulted in contracting muscles [26]. Finally in 1965 magnetical stimulation took a step when, according to the history reviews and their own later report, Bickford and Fremming were apparently the first to succeed in non-invasively stimulating a human nerve using magnetic fields. [9, 12, 21]

At this time electrical stimulation by feeding current into the tissue under stimulation was a generally used technique. Major draw-back of this method was, that it was *invasive*, meaning that the device providing the current needed to pierce the skin and thus caused pain. In 1973 Öberg et al. compared electrical to magnetic stimulation using frog's nerve and muscles. They reached a conclusion that magnetic stimulation could be used in therapy, where nerves need to be stimulated for long periods of time, and in studies of the nervous system. [34]

In 1980 Merton and Morton announced the success in electrically stimulating the cerebral cortex in a *non-invasive* (no need to pierce the skin) manner. This was apparently the first succeeded attempt to stimulate *transcranially*, which literally means 'through the skull'. They reported the phenomenon of phoshenes as well as muscle contraction [30, 31].

In 1982 Polson et al. were the first to successfully magnetically stimulate nerves of the arm non-invasively and both observe a twitch in thumb muscle and record it with EMG. They compared this with electrical stimulation and came to a conclusion that both methods produce similar method with magnetic stimulation being, in fact, less painful. Figure 11 shows the EMG responses of both magnetic and electrical stimulation. [37]

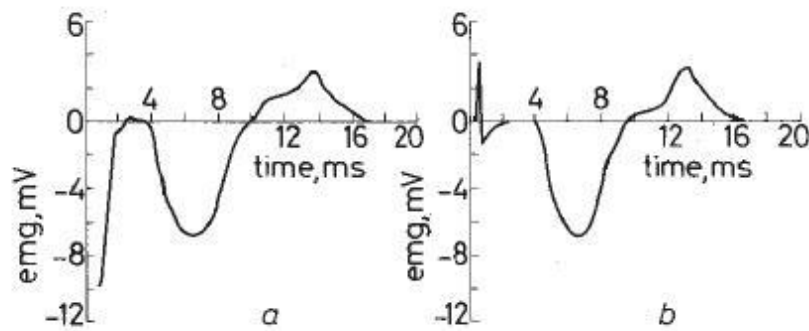


Figure 11: EMG responses measured from thumb muscle using (a) magnetic and (b) electrical stimulation. Figure from [37].

The idea of magnetic stimulation had been around quite long, but it was not until

1985 that Barker and his team were able to construct a magnetic stimulator powerful enough for this purpose. They were the first to succeed in stimulating the motor cortex and both observe a muscle twitch and measure the EMG response. They also stimulated the ulnar nerve in elbow to show that nerves in PNS could also be stimulated. Figure 12 presents the EMG results from their experiment. They argued that although electrical and magnetic stimulation resulted in similar results, using a magnetic stimulator was much easier and would thus be more suitable in clinical use. In addition, as the magnetic field passes through skull, the induced currents do not stimulate the pain receptors on skin thus making magnetic stimulation painless. [10]

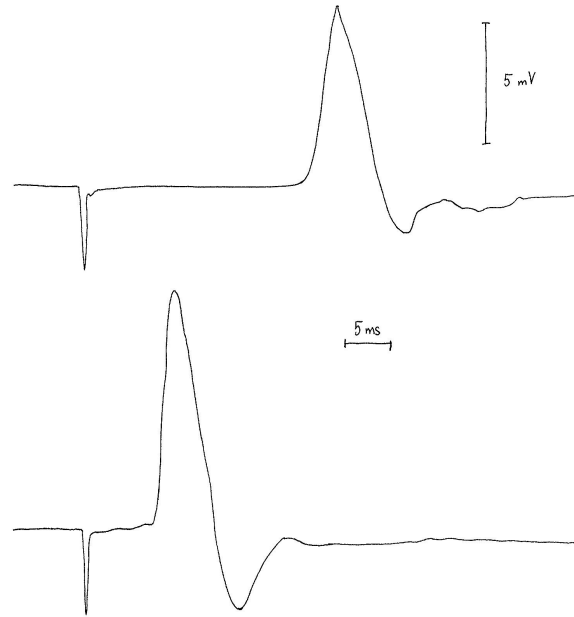


Figure 12: EMG responses measured from finger muscle, when stimulus was delivered in motor cortex (upper) and in motor nerve in elbow (lower). Figure redrawn from [10].

Since then, the development of magnetic stimulators has been intense and today, several different commercial devices are available for both clinical and research use. Figure 13 presents the magnetic stimulator used in Barker's experiment [10].

3.2 Underlying Physical Phenomena and Effects on Human Body

The basis of TMS lies in a physical phenomenon called *electromagnetic induction*, which is explained by Faraday's law (Eq. 3), but to understand how stimulation affects the body a little more is needed. Magnetic stimulator is an electrical device and so it is natural to start with Ampère's law (Eq. 4), which states that an electric current is surrounded by a magnetic field. Faraday's law then tells that the opposite is true only when the magnetic field changes with time. Furthermore, Ohm's law

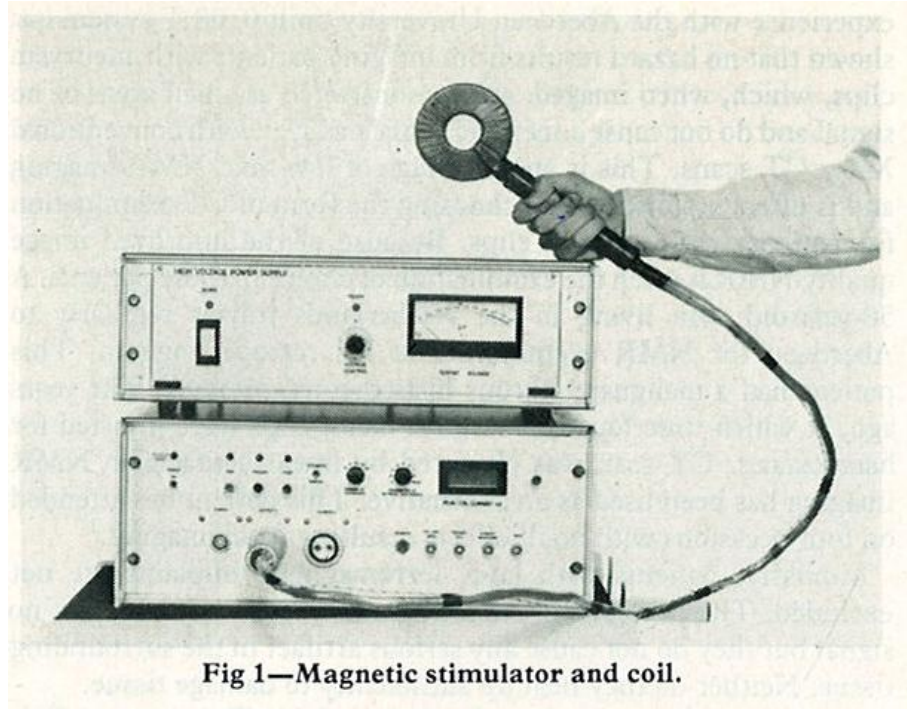


Figure 13: Magnetic stimulator used in Barker's study. Figure from [10].

(Eq. 5) connects current to electric field through material's conductivity. If the material is a perfect dielectric ($\sigma = 0$), the no current can be detected no matter how strong an electric field is applied.

$$\nabla \times \mathbf{E} = -\frac{\partial \mathbf{B}}{\partial t} \quad (3)$$

$$\nabla \times \mathbf{H} = \mathbf{J} + \frac{\partial \mathbf{D}}{\partial t} \quad (4)$$

$$\mathbf{J} = \sigma \mathbf{E} \quad (5)$$

,where \mathbf{E} is electric field intensity
 \mathbf{B} is magnetic flux density
 t is time
 \mathbf{H} is magnetic field intensity
 \mathbf{J} is current density
 \mathbf{D} is electric flux density
 σ is conductivity of the material

From these laws one is able to conclude that an *alternating current* (AC) produces a time-varying magnetic field, which then induces an electric field. If the materials conductivity is proper, a current is also generated. The currents produced in this manner are called *eddy currents*. There need not be any conducting material between

the AC carrying wire and the material in which the eddy currents can be detected. Linkage can be reinforced by using for example a piece of iron to guide the magnetic field. [17, 40, 48]

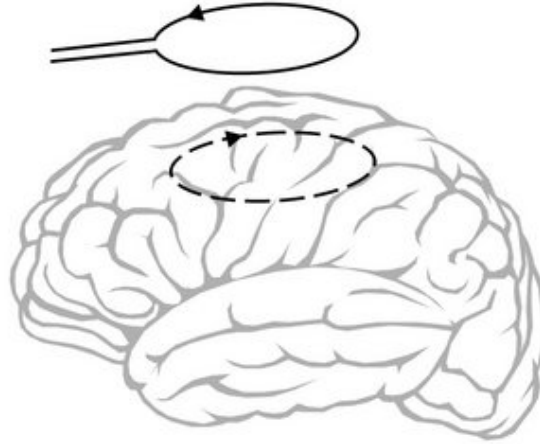


Figure 14: Above the brain is a AC-carrying loop. Dashed line shows the eddy currents induced in brain. Arrows show the directions of the currents. Figure from [7].

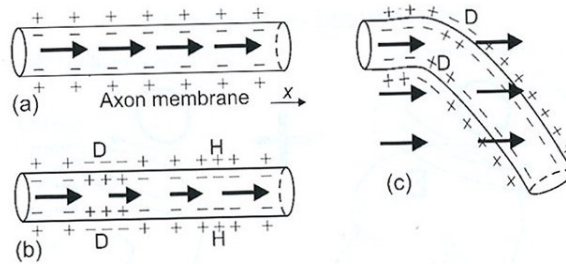


Figure 15: The effect of electric field (pattern visualized with arrows) on axon membrane. a) Uniform \mathbf{E} along an axon; b) changing \mathbf{E} along axon; and c) uniform \mathbf{E} on a bent axon. D and H mark the regions of depolarization and hyperpolarization, respectively. Figure from [39].

As the magnetic field passes through skull easily and the brain is conductive material, eddy currents are generated in the cerebral cortex (Figure 14). If the currents manage to depolarize a neuron's membrane enough, then an action potential is generated. Studies have shown that the electric field intensity should be around 100 V/m. Figure 15 shows how the electric field affects the neuron axons. Additionally, the neurons located in the PNS can be stimulated. [39, 40] The probability of exciting the right neurons is affected by the random firing of neurons and the following refractory period.

It must be noted, that although the name of this stimulation technique implies that the magnetic field stimulates, this is in fact not the case. Magnetic field provides a way to evoke an electric field and thus generate action potentials in the brain without directly feeding current on tissue. [8] Geddes has suggested this stimulation technique be called *electrodeless stimulation* as opposed to electrical stimulation, where electrical current is induced in the brain through electrodes. [20]

3.3 Modern-day Stimulating Equipment

This section introduces the parts of a modern-day TMS device using the eXimia NBS (Navigated Brain Stimulation) system (Figure 16) manufactured by Nexstim Ltd as an example. Commercial stimulators differ from each other slightly. Common to them all are the stimulator and coil. This chapter also introduces EMG and navigation, both of which are integrated in eXimia NBS but may be separate in other systems. Furthermore, only equipment related to this study (Chapter 5) are presented.

Magnetic Stimulator

Figure 17 presents the basic circuit of a magnetic stimulator. Before a pulse can be generated, the stimulator needs to be charged. This happens by closing the switch (S1), when the energy from the power supply (V) is stored in the capacitor. Once the capacitor is fully charged, the switch (S1) is opened and thyristor switch closed allowing the capacitor to discharge and current flowing through the stimulating coil. Diode (D) and resistance (R) are used to control the damping of the magnetic field. [9]

Stimulators produce different types of pulse waveforms: *mono-* and *biphasic* (Figure 18). In addition, there are three different types of stimulation: single pulse, paired pulse, and repetitive TMS (rTMS). [39]

This study was carried out using single pulse stimulation and a biphasic waveform.

Coils

The shape of the coil has a large impact on the stimulated area on the cerebral cortex. Two of the commonly used coil shapes are circular and figure-of-eight. The electric field strengths induced by these coils are seen in Figure 19. Circular coils induce an electric which is strongest under the circumference of the coil, whereas the electric field induced by a figure-of-eight coil is strongest in the middle thus being more focal. This has an impact on how the coil should be positioned in order to stimulate the target area. In addition, the electric field induced by a circular coil penetrates deeper than the electric field induced by the figure-of-eight coil. [39]

This study was conducted using the figure-of-eight coil.



Figure 16: Nexstim eXimia NBS System with integrated EMG (Courtesy of Nexstim Ltd.).

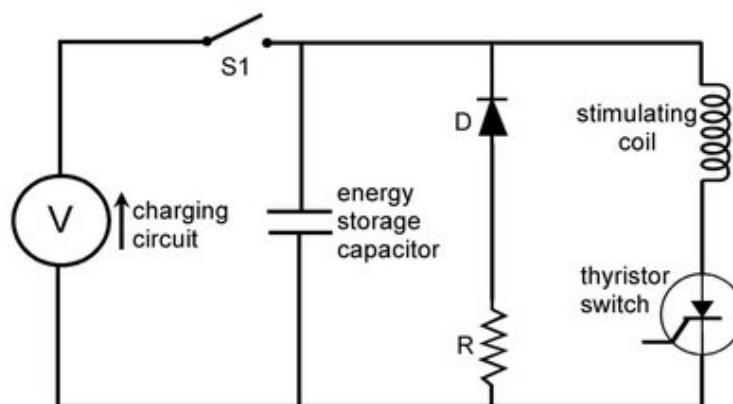


Figure 17: Basic circuit of a magnetic stimulator. Figure from [7].

Electromyography

EMG is a technique for measuring the electrical activity of muscles. Electrodes are placed over the target muscle (Figure 20) and when the corresponding area on

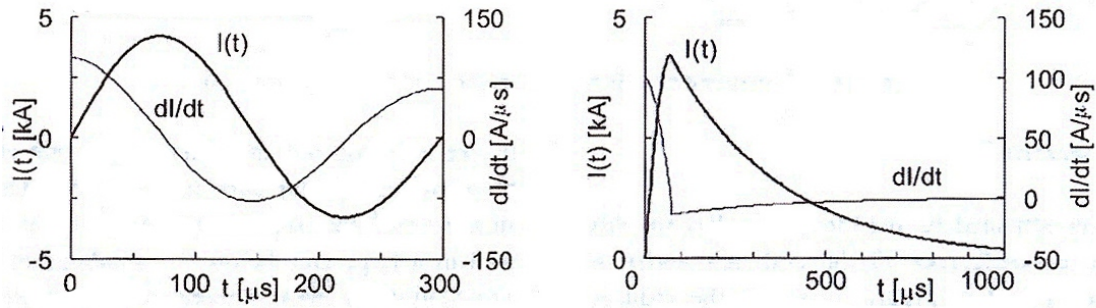


Figure 18: Types of pulse waveforms. Biphasic on the left and monophasic on the right. Current I and its rate of change dI/dt are shown. Figure modified from [39]

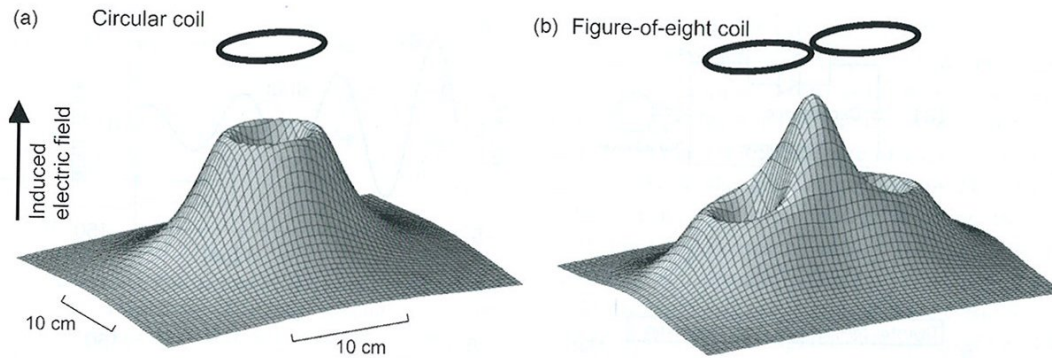


Figure 19: Schematics of different coil designs and the electric field strengths they induce. Figure from [39]

the motor cortex is stimulated, the electrodes detect the electrical activity in the muscle, if there is any. Hence, one is able to see if there is activity without the need to observe the actual muscle twitch. Usual follow-up measures of this activity are the *latency* and *peak-to-peak amplitude*. Latency tells the how long it takes for the signal to travel to the target muscle and peak-to-peak amplitude tells the strength. [29] Usually the goal is to find out whether there are responses or not. The *amplitude threshold* (i.e., minimum level) for this is in most cases $50 \mu\text{V}$. [29]

Navigation

For the stimulation to be effective, the stimuli (i.e., pulses) need to be delivered on the target area with suitable strength. The strength of the induced electric field is

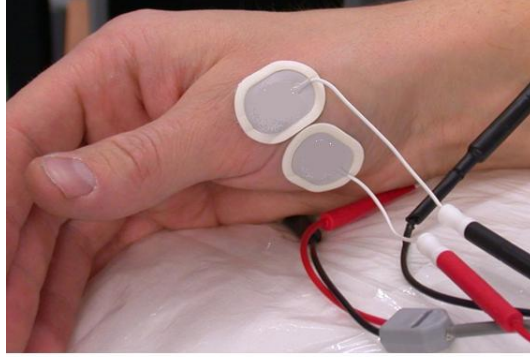


Figure 20: Electrode placements on the right hand thumb muscle. (Courtesy of Nexstim Ltd.)

not solely dependent of the stimulator intensity used but also the position of the coil. A study announces that increasing the coil-cortex distance has a decreasing effect on MT [41]. Thus, it is important to be able to repeat stimulation at the same location accurately. Navigation helps to position the coil such that the induced currents stimulate the desired area.

In navigated TMS a navigation software constructs a three-dimensional (3D) model of the patient's head using magnetic resonance (MR) images. The patient's head and the model are co-registered using a tracking system (Figure 21). The software calculates generated electric field strength on the brain at user-chosen depth real-time. [27]

3.4 Usage and Safety

Besides studies of the nervous system of humans and other animals, TMS is used in therapy and studies concerning effects of disorders. Studies of the nervous system include research concerning both *in vivo* (living) and *in vitro* (partial or dead) organisms. A unique technique is producing 'virtual lesions' in brain, thus seeing how the brain functions are organized. Therapy includes treatment of pain, migraine, and some psychiatric conditions, such as depression. Multiple sclerosis (MS) and stroke are examples of disorders affecting the movement. In addition, TMS is used in presurgical planning for tumor resectioning. [36, 49]

Although TMS is considered a safe mode of stimulation as it is pain-free, there are still some issues to be taken into account both in stimulator design and operation. The coil might heat up causing discomfort or even skin burn to the subject. Furthermore, delivering a stimulus produces a loud clicking-noise, which should be noted especially if the coil is placed near the ears. [38]

There are very little known adverse effects of TMS. One possible effect are seizures following the usage of high-intensity rTMS. Subjects having metallic objects (such as pacemakers, cochlear implants, or even shell fragments) inside them, are at risk of



Figure 21: Tracking system (Courtesy of Nexstim Ltd.).

physical damage due to magnetic fields that might cause these objects to move. However, as the technique is relatively new, there is no knowledge of possible long-term effects. Thus, further research is required and the research and clinical communities need to be alert. [36]

In addition, stimulus strength usually is announced as *percentage of stimulator output* (PSO) for there are many variables to be considered and a universal unit has not been formed yet. [38] However, due to differences in stimulator designs, two stimuli having the same PSO cannot be considered identical straight away. Additionally, the design of the coil has an effect. Therefore, if, for instance, stimulator A was used in stroke therapy one day, then stimulator B cannot be used with the same PSO until it has been verified that these are, in fact, close enough.

3.5 Summary

TMS is based on a physical phenomenon called electromagnetic induction, which explains how a time-varying magnetic field (produced by the stimulator) generates eddy currents in a conducting material (the brain). These eddy currents affect the membrane potential of neuron axons such that action potentials are generated and signals flow from the cortex to the target muscle.

The first magnetic stimulators were not powerful enough to stimulate anything else but the retinal cells and producing a visual phenomenon called phosphenes. Stimulating peripheral nerves was successful for the first time in the late 1960s. The first magnetic stimulator capable of transcranial stimulation was manufactured in 1985. Since then the development has been ongoing.

A modern-day magnetic stimulator consists of a stimulator and a coil. Stimulators are capable of producing either mono- or biphasic pulse waveforms. Most often used coil designs are circular and figure-of-eight. Other appliances used are EMG device, for detecting electrical activity in the muscle; and navigation, aiding in accurate repetition of stimuli.

TMS is used in studies of the nervous system and effects of disorders; therapy; and presurgical planning. Heating of the coil, and stimulator noise need to be taken into account when stimulating. Furthermore, due to differences between different stimulators and coils, caution must be taken to ensure that produced stimulus intensities are identical.

Seizures are one known adverse effect, but has been encountered rarely. In addition, patients having any metallic implants must not be exposed to magnetic fields, due to the risk of these objects moving.

4 Motor Threshold

Psychophysics studies the relationship between a presented stimulus and the observer's perception of it. *Absolute threshold* is a central concept, which means the minimum stimulus intensity required to enable the observer to perceive it. Since biological systems are constantly changing, the threshold cannot be a single value but rather has a statistical nature. Typically the threshold has been defined as the stimulus intensity which is perceptible in 50% of trials. [22]

Many of the techniques used in psychophysics have been incorporated in the definition and determination of MT, as the threshold provides a measure for quantifying the sensitivity of sensory systems.

This chapter introduces the concept of MT. First, the definition and usage are explained. Then, four different estimation methods are presented. Finally, as this study compares these different procedures, previous studies on the same topic are discussed.

4.1 Definition and Usage

MT is a measure which is believed to express cortical excitability. It is defined as the stimulator intensity using which a response is detected in the target muscle with probability $p = 0.5$ [6, 10, 47] and is (usually) expressed as PSO in the range of 0 – 100%. This measure is used in deciding the dosage (i.e., the intensity to use) for stimulation, for example stroke therapy using rTMS. [50] MT is estimated for a target muscle, which can either be at rest (rMT) or under constant tension (aMT). [38]

Estimating rMT is recommended since it might be difficult to keep the target muscle under constant tension. Furthermore, aMT is generally lower than rMT and this could result in too large a dosage of TMS if treatment is given while patient is at rest. [13, 38, 49] One study suggests that instead of PSO intensity, MT should be announced as the strength of the induced electric field. Current way ties MT to the equipment with which it was determined and dosage cannot necessarily be solely decided based on the MT value. [15]

Studies suggest, that, although subject-specific, MT is not a stable measure throughout life. It is apparently affected by conditions such as age, hormonal activity, and awareness level. In addition, some disorders (such as MS) affect MT. [13, 49]

Futhermore, Mills and Nithi prefer the term "corticomotor threshold" over MT, since they believe that factors affecting the threshold value can be either cortical or spinal. [32]

As it was mentioned in Chapter 2, simply thinking of moving a muscle or watching someone else move that muscle activates the same neurons, which would activate when actually moving the muscle. When this piece of information is added to that of a refractory period during which the neuron is unable to fire, one could conclude

that these might affect the MT. However, no research on this matter exists.

In depression therapy the MT of the right thumb muscle is estimated to define the proper dosage [1]. However, in the actual therapy, the left frontal lobe is stimulated. Studies have shown that different muscles have different MT values [6,38]. It seems peculiar, that this MT is used as the base for the therapy stimulation.

4.2 Estimation of Motor Threshold

There are a number of ways to estimate MT, however, a stable standard way has not been formed. In this chapter, four different methods are explained more closely: Rossini-Rothwell, MN, AML, and NML.

A response is defined either being a visible twitch in the target muscle or using an EMG measuring device, a MEP strong enough. The threshold for MEP strength varies, but is usually set to $50 \mu V$, when estimating rMT. For aMT, the amplitude threshold is considerably higher, around $200 - 300 \mu V$. [38]

International Federation of Clinical Neurophysiology (IFCN) suggests that subjects "keep their eyes open and perform simple calculations" during experiment to ensure that level of awareness stays constant. [38]

Rossini-Rothwell

The Rossini-Rothwell method is the original IFCN recommendation. It does not include an explicit procedure for the MT determination. First, the *hot spot* for the target muscle is located by moving the coil over the motor cortex while stimulating. The hot spot is defined as the location on the cerebral cortex where a response in the target muscle is detected with the lowest intensity and shortest latency. Then, stimulating at this location the stimulus intensity is increased in 5 PSO steps until a level where approximately 50% of 10-20 consecutive stimuli elicit a response. They define a response as MEP around $100 \mu V$. [38] Five responses out of 10 stimuli is the usual practise.

This method is introduced here as it is the first attempt to define a way to estimate MT. Due to its vague nature and reliance of operator experience it was left out from this study.

Mills-Nithi

MN method employs a specific bookkeeping method, where a table of 100 rows (PSO) and 10 columns is filled during estimation. The first available cell in the row corresponding to the used stimulator intensity used is marked with a running number of the stimulus and whether there was a response or not. An example is shown in Figure 22.

The protocol has three parts:

1. Find approximate threshold (AT)

Stimulation is started from intensity level of 20 PSO of stimulator output.

Intensity is increased in 10 PSO steps until a response occurs. This intensity level is marked as AT.

2. Find lower threshold (LT)

Part two starts from AT level.

Intensity is decreased in 1 PSO steps until no response occurs. An attempt to deliver 10 consecutive stimuli eliciting no response is made. If the attempt fails, the intensity is decreased by 1 PSO until such a level is found or the intensity drops to 0 PSO.

3. Find upper threshold (UT)

Part three starts at the lowest intensity level where a response was detected in the beginning of the second part.

Intensity is increased in 1 PSO steps until a response occurs. An attempt to deliver 10 consecutive stimuli all eliciting a response is made. If the attempt fails, the intensity is increased by 1 PSO until such a level is found or the intensity is increased to 100 PSO.

MT is then defined as the arithmetic average of LT and UT as Equation 6 shows.

$$MT = \frac{LT + UT}{2} \quad (6)$$

A response is defined as a MEP having latency of $17 - 30 \text{ ms}$ and amplitude over $20 \mu V$.

This method was not designed to show the intensity level of 0.5 probability, but, the developers believe that, if there is ever need for one single estimate, then the average of intensities where responses are guaranteed and where they do not exist is sufficient. [32]

Awiszus (Maximum Likelihood)

AML method is based on the probability distribution of the responses. This method attempts to estimate the distribution based on intensity values used in stimulation and the responses they generate. The method is developed using a "best parameter estimation by sequential testing" (best PEST) strategy.

The probability for a response is modeled as cumulative Gaussian

$$p(m, t, s) = \frac{1}{s\sqrt{2\pi}} \int_{-\infty}^m e^{\frac{(\tau-t)^2}{2s^2}} d\tau \quad (7)$$

Intensity (%max)	TRIAL NUMBER									
	1	2	3	4	5	6	7	8	9	10
15										
16										
17										
18										
19										
20	1									
21										
22										
23										
24										
25										
26										
27										
28										
29										
30	2									
31										
32										
33										
34										
35	35	36	37	38	39	40	41	42	43	44
36	28	29	30	31	32	33	34			
37	27									
38	21	22	23	24	25	26				
39	18	19	20							
40	3	17								
41	18									
42	12	13	14	15						
43	11	45								
44	10	46								
45	9	47								
46	8	48								
47	7	49	50							
48	6	51	52	53	54	55	56	57		
49	5	58	59	60	61	62	63	64	65	66
50	4									
51										
52										
53										
54										

Lower Threshold

Upper Threshold

Present
 Absent

Figure 22: An example of MN bookkeeping method. The complete table has intensity levels 0 - 100 % [32]

where m is the stimulus intensity

t is threshold (i.e., stimulus intensity with which $p = 0.5$)

s is threshold spread (i.e., additional stimulus intensity required to achieve $p = 0.84$)

Equation 8 presents the log-likelihood function used in estimation process. Function is divided in two, as in a total of $n = j + k$ trials, j stimuli elicit a response and k do not.

$$L(t, s) = \sum_{i=1}^j \ln(1 - p(ms_i, t, s)) + \sum_{i=1}^k \ln(p(mf_i, t, s)) \quad (8)$$

where ms are intensities eliciting a response

mf are intensities incapable of eliciting a response

t is the maximum likelihood threshold estimate

s is the maximum likelihood threshold spread estimate

t and s maximize the log-likelihood function. [6]

The estimation protocol itself is simple. Algorithm suggests a stimulus intensity to use (i.e., t , which maximizes $L(t, s)$) and user reports whether a stimulus having this intensity elicited a response or not. There is no ending criterion and thus the decision on when the estimate is reached rests upon the user.

New Variant of Maximum Likelihood

NML method was developed using the maximum likelihood approach. Parameters were chosen in order to improve speed while maximizing the log-likelihood. In addition, this method aimed to take into account subject's anticipation of stimuli by varying the probability of responses at different parts of stimulation. No ending criterion was implemented.

The estimation protocol was the same as in AML.

4.3 Previous Comparison Studies

Awiszus conducted a study where he compared his own AML method against MN and Rossini-Rothwell procedures. First, using his method and two different coils he measured MTs (amplitude threshold for a response was $50 \mu V$) for a total of 28 different muscles to determine a range of stimulus intensities. Then, in data collection step, the subjects were stimulated such that each intensity level was used 50 times in a randomized order. Finally, the collected data were used in simulation comparing the three methods. The report does not mention what ending criteria was used when employing the AML method, although, mentions, that in simulation 10 to 50 stimuli were used. MN was implemented as the developers intended. Rossini-Rothwell was implemented such that 10 stimuli were used at each intensity level and lowest intensity with 5 or more responses was selected as MT. He reached a conclusion that the AML method was superior in both accuracy and number of stimuli when compared to the other methods. The Rossini-Rothwell method performed worst. [6]

Mishory et al. compared AML method against MN, which they falsely identify as IFCN recommendation. AML method was run using the software provided by the developer and ended when two subsequent estimates were the same. MN was modified such that the starting intensity was 50 PSO. LT was determined by decreasing the intensity in 2 PSO steps from the starting intensity to an intensity level where less than three out of six trials elicited a response. Similarly, UT was defined increasing from the starting intensity with 2 PSO steps to a level where response was detected in three out of six trials. The MN bookkeeping methods was applied: all six trials were not necessary if a condition to either stop or move on was reached. Furthermore, Awiszus method was automated such that the algorithm received input directly from the EMG measurement device (amplitude threshold for a response $100 \mu V$) and directly controlled the TMS device. There was also another study

where visible twitch was used instead of the EMG measurement. They reached a conclusion that AML method performed faster with fewer stimuli. [5]

Tranulis et al. also compared three methods against each other: Rossini-Rothwell, MN, and their own "supervised parametric method". Responses were measured using EMG device (amplitude threshold was $50 \mu V$). Rossini-Rothwell method started from intensity level of 90 PSO. Intensity was decreased in steps of 5 PSO until one out of 10 stimuli elicited a response. Then, intensity was increased in 2 PSO steps until an intensity level where five or more stimuli out of 10 elicited a response. This intensity was declared MT. MN procedure started from intensity level 10 PSO. Intensity was increased in 10 PSO steps until a level where one out of 10 stimuli elicited a response. LT was defined from this level by decreasing the intensity in 1 PSO steps until no responses occurred within 10 trials. UT was found starting from intensity level of 90 PSO and decreasing in 10 PSO steps until less than 10 responses out of 10 trials occurred, then increasing until all 10 trials elicited a response. MT was determined as the arithmetic mean of LT and UT. The bookkeeping method was not applied: all 10 stimuli were given. Their own method started from intensity level 10 PSO. It was increased in 10 PSO steps until one trial out of 10 elicited a response. Then, starting from previous level, intensity was increased in 2 PSO steps until two consecutive intensities resulted in 10 responses out of 10 trials. A curve was fitted to these results and MT was determined to be the intensity where $p = 0.5$. The suggestion was confirmed by one of the researchers before accepting. Their results indicate that there was no significant difference between these methods. Although, Rossini-Rothwell performed with least amount of stimuli. [47]

4.4 Summary

MT is used as a measure of cortical excitability, but there exists no standard way to determine it. Common for all determination methods is that they all seek an intensity level, where half of given stimuli will elicit a response and half will not. There are also differences in response definitions. Some use visible twitch -method and some an EMG device. Usually a response is defined using the MEP level of $50 \mu V$ as the amplitude threshold for rMT, whereas estimating aMT the amplitude threshold is $200 - 300 \mu V$.

Four different methods were explained in detail: the Rossini-Rothwell, MN, AML, and NML. The goal in the first method is to find the intensity level where five out of ten stimuli elicit a response. The second finds two intensity levels, LT and UT and defines MT as the average of these. The third and fourth are purely mathematical methods which try to estimate the true probability distribution of the responses.

Three previous comparison studies were introduced. It seems, that no other study has compared estimation methods thoroughly using both simulation and stimulated subjects. One study used subjects for data collection, but compared the estimation methods only with simulation. Furthermore, the MN method has been modified in almost all studies. Additionally, each include their own version of Rossini-Rothwell.

One study introduced another kind of mathematical approach. EMG measurements were used in all studies and one additionally included the visible twitch -method.

The results of these studies vary. Two conclude that AML performed best (number of stimuli, faster time, or accuracy), whereas one suggests that there were no significant differences apart from Rossini-Rothwell performing with least stimuli.

5 Methods

The objective of this study was to compare three different determination protocols introduced in section 4.2: MN, AML, and NML. From previous studies it was known how the MN and AML compare, but this study hypothesized that the modifications of NML would cause it to perform better than AML.

The comparisons were performed both in simulation and navigated TMS. Simulations were carried out at Nexstim headquarters in Helsinki and TMS experiments took place in Kuopio University Hospital (KUH) in Kuopio.

This chapter describes the methods and analysis techniques used.

5.1 Simulations

Simulations were designed to test the accuracy of the estimation methods. Algorithms were implemented in MATLAB (version 7.1.0.246(R14)) program and run without human input. Source code was proofread in order to prevent any errors caused by the programmer. Simulations were run in a Windows XP (SP2) environment with no other programs running simultaneously.

Simulation routine was divided into two parts. The first part simulated the MT estimation for several different subjects and the second part simulated the repeated MT estimation of a single subject. The simulations assumed that the MT of a single person is constant and that every MEP would be acceptable. Both parts contained 160000 estimations per method totaling in 640000 runs.

A "true motor threshold" (tt) was generated by randomly sampling from the uniform distribution ($tt \sim U(0.25, 0.75)$). The range of the distribution represents the range where MT values are usually found. Values represent PSOs in the range of 0 – 1. Resulting MEPs were simulated such that when Equation 9 was true then a response occurred.

$$v < p(m, t, s) \tag{9}$$

where v is a random variable $v \sim U(0, 1)$
 $p(m, t, s)$ is cumulative Gaussian (Equation 7)

In these simulations all estimation methods were ensured to find the same true thresholds in the same order. Additionally, since there is no real human subject who might become tired or in some other way interfere with the measurements, simulating is a reliable method for purely comparing the methods' performance.

5.2 Navigated Transcranial Magnetic Stimulation Study

5.2.1 Subjects

Five right-handed healthy subjects volunteered to participate in the navigated TMS study. They all gave written consent and the study was also approved by the local ethics committee. All subjects were familiar with TMS and had been participating in measurements before.

5.2.2 Equipment

MRI was performed prior to the experiment with a 1.5T Siemens Magnetom Avanto (Erlangen, Germany) using a T1-weighted sequence (TR 1980 ms, TE 3.93 ms, FOV 256 mm, matrix 179 x 256, slice thickness 1.0 mm, and spatial resolution of 1.4 mm x 1.0 mm x 1.0 mm).

Stimulation was performed using eXimia NBS system (Nexstim Ltd, Helsinki, Finland), which consisted of a TMS stimulator, navigation software (version 3.2.1), and EMG recording device (described in Section 3.3). MEPs were recorded using surface electrodes (Ambu Neuroline 720 (lead wire 10 cm, connector type K)). A Focal BiPulse figure-of-eight coil was used. A response was defined as MEP over the amplitude threshold of 50 μV .

All estimation methods were implemented as small computer programs designed to guide the operators. All suggested an intensity to use for the next stimulus and the operator reported whether there was a response or not. The operators performing the stimulation were not involved in the programming and were not aware of which methods they were testing. The estimation methods' program codes were the same as used in the simulation step. The user interfaces were designed such that the operator would have no clue of the estimation method. The programs were run on a separate computer in a Windows XP (SP2) environment with no other programs running to ensure the calculation capacity was available.

5.2.3 Stimulation Protocol

In navigated TMS study all three methods were compared against each other in finding the rMT for the right hand APB. Two operators were involved in every session: one stimulated with the TMS while the other used the external computer and the estimation programs. There were a total of five operators involved, all of whom were experienced TMS users.

A preliminary mapping was performed on each subject to find the best stimulation location (i.e., hot spot) for the APB of the right hand. The same hot spot was used in every estimation process (Figure 23). A separate coil support was not needed to ensure the stability of the stimulation location due to the navigation software, which allows the user to repeat stimulation in one spot accurately.

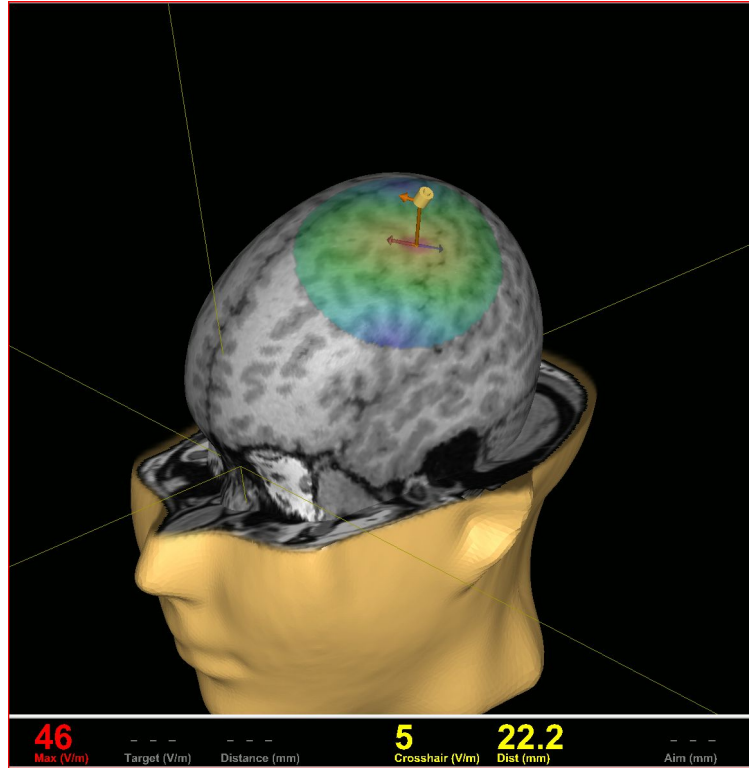


Figure 23: Location of the hot spot of one subject as seen in NBS. The small cylinder marks the location of the coil on the scalp. The red arrow (on cortex) and orange arrow (bottom of the cylinder) show the direction of the electric field. Electric field strength is shown as the colored circle on the cortex. (Courtesy of Nexstim Ltd.)

Subjects were instructed to sit relaxed in a chair with their eyes open. Right hand was supported with a pillow and kept in supine position. Subjects were allowed to move during the breaks, after which co-registration was checked. Operators discarded stimuli where EMG showed tension before MEP, when subject was clearly not alert at the time of the stimulus, or when operator suspected that the coil was positioned falsely.

Estimation methods were run always in the same order (NML, MN, AML). A total of two rounds were completed. A short break was taken between estimation processes to prevent possible effects caused by the previous stimulation.

MN was run until MT had been acquired whereas NML and AML methods were stopped after 20 stimuli.

In order to keep all possible variables constant all subjects were right-handed and MT was estimated only for right-hand APB. In addition, estimation processes were run in the same order such that the subjects becoming tired would show similarly in all results.

5.3 Data Analysis

Results from simulation and TMS steps were analyzed separately. The aim was to find the best implementable method for MT estimation. As the technical aspects (i.e., the amount of code or the computers ability to calculate fast enough) were not of issue, the methods themselves need to be analyzed.

Simulation

The results from the simulation tests were analyzed using MATLAB (version 7.1.0.246 (R14)). NML and AML performances were analyzed after 20 stimuli. Results from the two parts were averaged.

The average difference along with minimum and maximum differences between estimates and tt were calculated to see the accuracy of the methods. In addition, the percentage of exact matches (i.e., difference less than 1 PSO) was calculated for all methods.

The precision of the methods was tested by calculating the absolute differences and their minimum and maximum values between the estimates of all methods.

To provide other measures for comparison, the number of stimuli used (on average, minimum, and maximum) in MN method was calculated.

Navigated Transcranial Magnetic Stimulation Study

Wilcoxon Rank Sum Test was used to test that all methods produce estimates from the same probability distribution.

The precision of the methods was tested by calculating the absolute differences and their minimum and maximum values between the estimates of all methods.

To provide other measures for comparison, the number of stimuli used (on average, minimum, and maximum) in MN method was calculated. Furthermore, the estimation time was reported (on average, minimum, and maximum).

5.4 Summary

The objective of this study was to compare three different estimation methods against each other in order to select the best method to be implemented as a computerized tool. The selection was based on the following characteristics: accuracy, precision, number of stimuli used, and the estimation time.

The study was divided in two. The first part was a simulation and the second part was a navigated TMS study. All three methods (NML, MN, and AML) were compared against each other. Navigated TMS study involved five voluntary subjects and a total of five operators, two of whom were present in each session at a time.

Results were statistically analyzed according to the characteristics of interest.

6 Results

This chapter presents results from the study introduced in Chapter 5. The objective was compare different estimation method in order to find the best to be implemented as a computerized tool. Results are grouped according to the followed characteristics and presented in Tables 3 to 6 and Figures 24 to 25.

Unfortunately, due to unavailable source code, AML could not be included in the simulations. Moreover, Navigated TMS study had to be conducted such that for AML a program available from the developer was used. The software had the identification information printed, resulting in recognition of the method as the operators had used the same program before. NML and MN remained unknown. In addition, AML was run only once per subject. Therefore, results contain AML estimates only half the number of NML and MN estimates.

Wilcoxon Rank Sum Test was performed on the estimates from the TMS study such that all were tested against each other. There were no significant differences ($p < 0.05$) between the estimates and it can be said that all estimates are samples from the same probability distribution regardless of the estimation process.

Table 3: Results connected with accuracy: absolute difference between estimates and tt presented as PSO; and percentage of exact matches (i.e., absolute difference less than 1 PSO).

	Test 1	Test 2
Absolute difference		
$ NML - tt $ (mean \pm std)	0.83 \pm 0.72	1.00 \pm 0.77
min	0.00	0.00
max	8.67	6.26
$ MN - tt $ (mean \pm std)	0.93 \pm 0.75	1.05 \pm 0.86
min	0.00	0.07
max	8.52	9.07
Exact matches		
NML	68.46%	58.33%
MN	62.08%	59.53%

Table 4: Results connected with precision: absolute difference between estimates presented as PSO. '-' means that measurement was not available.

	Test 1	Test 2	TMS study
$ NML - MN $ (mean \pm std)	1.23 \pm 1.00	1.42 \pm 1.08	1.47 \pm 1.33
min	0.00	0.00	0.00
max	10.13	8.93	3.92
$ NML - AML $ (mean \pm std)	-	-	1.81 \pm 1.07
min	-	-	0.18
max	-	-	5.22
$ MN - AML $ (mean \pm std)	-	-	1.11 \pm 1.40
min	-	-	0.03
max	-	-	4.81

Table 5: Number of stimuli used in MN process. NML and AML were always run using 20 stimuli.

	Test 1	Test 2	TMS study
average	55	61	51
min	24	25	33
max	130	126	75

Table 6: Estimation times from TMS study.

	NML	MN	AML
average	< 7 min	< 8 min	< 5 min
min	< 4 min	< 5 min	< 5 min
max	< 10 min	< 12 min	< 8 min

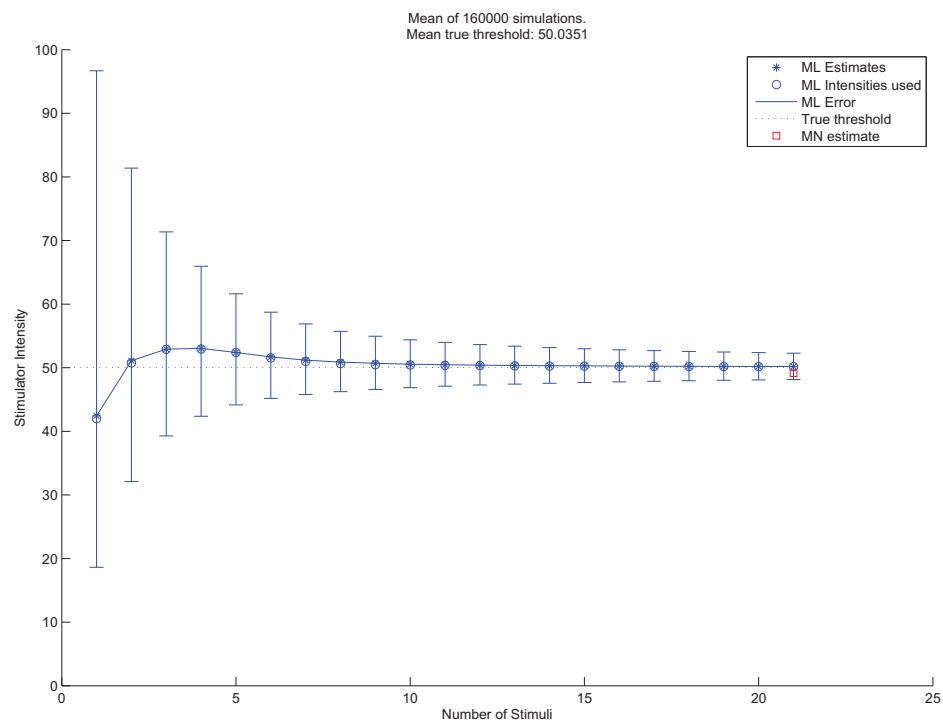


Figure 24: Average run of simulation test 1. MN estimate is presented next to NML estimate regardless of stimuli used.

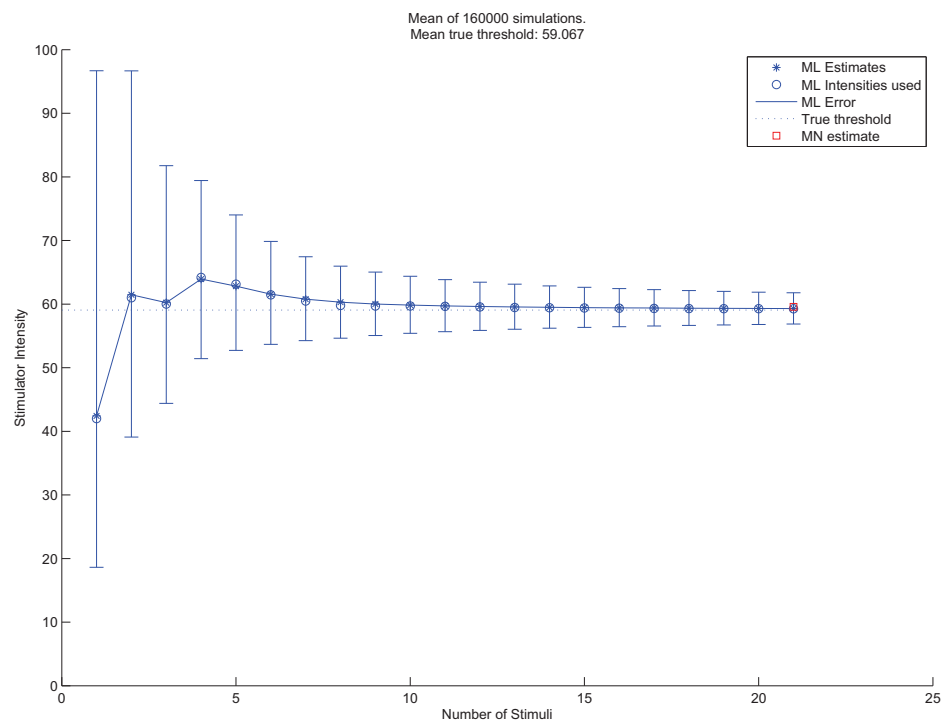


Figure 25: Average run of simulation test 2. MN estimate is presented next to NML estimate regardless of stimuli used.

7 Discussion

The objective of this study was to compare different MT estimation methods in order to find the best to implement as a computerized tool. Only methods having a clear implementable algorithm were chosen to this comparison. Then, the best method was searched by focusing on the following characteristics: accuracy, precision, number of stimuli used, and the estimation time. Results are displayed in Chapter 6.

Table 3 presents accuracy-related results. It can be seen, that both NML and MN methods are quite accurate in finding the true threshold. Estimate was correct in around 60% of cases and average difference between the estimate and true threshold was around 1 PSO and the standard deviation was around 1 PSO. However, the maximum difference was disturbingly large, ranging between 6 and 9 PSO.

Table 4 shows precision-related results. Based on these and the result of Wilcoxon Rank Sum Test, the methods can be said to be precise. Average difference between estimates was below 2 PSO as was the standard deviation. The minimum difference found was below 0.20 PSO at highest. The maximum difference ranged between 4 and 10 PSO. In addition, it seems that simulation produced less precise estimates than the TMS study.

As NML and AML methods were run using fixed number of stimuli, only the number needed by MN method is relevant in comparison. Results in Table 5 show, that MN needs over 50 stimuli on average. There were differences between simulation runs and TMS study: simulation runs needed over 120 stimuli at most.

All estimation processes were completed under 8 minutes on average (Table 6), with the AML being fastest (under 5 minutes) and MN the slowest (under 8 minutes).

These results coincide with previous, more restricted, studies in that there were no significant differences between methods. MN required the most stimuli and AML method performed fastest (on average).

The solution to the problem of finding the best implementable MT estimation method was found only partially. It seems that from these three methods any one could be chosen if the criterion is merely the precision of the final estimate. However, if the number of used stimuli or the estimation time matter, then MN is not the best choice. In addition, both maximum likelihood methods might be able to reach an adequate estimate with fewer stimuli than the fixed amount of 20 used in this study. Figures 24 and 25 show, that NML reached an adequate estimate around 10 stimuli.

At least the following matters have an effect on MT: age and gender of the subject, as well as the awareness level. However, as this study aimed to compare the estimation methods themselves, the variability of the MT should not affect the results.

On the other hand, results of this study may have been affected by several causes. The operators in TMS study were experienced users. This might shorten the average estimation time. In addition, they were familiar with AML method and had been

using the same software before. Although, NML method performs in a very similar manner they did not report recognition. Furthermore, the operators were apparently familiar with the subjects as well. Being able to guess the algorithm's next suggested intensity and the strength of the resulting MEP might speed up the process.

This study relies on several assumptions.

1. Simulations and TMS measurements are comparable

If not, accuracy could not be measured from this study.

2. Methods can be compared reliably even if the hot spot location is wrong

Even though the actual MT value is not interesting a wrong hot spot location could cause the MT value to be higher than usual affecting the variability and thus precision.

A wrong location could also affect the number of stimuli needed in MN method.

However, as this study was conducted using navigated TMS, all methods were repeated exactly on the same hot spot. Previous studies did not use navigation meaning, that the running different procedures on the same location might have been unsuccessful.

3. MEPs can be simulated using (Eq. 9)

This study was limited to include only methods of which there was an explicit algorithm described. Additionally, not all available choices for MT estimation were searched. Therefore, there might exist an even better estimation method. The fixed number of stimuli in maximum likelihood methods prevented these methods from showing their true abilities. The operators did report, that it was frustrating to change the intensity between two intensities only because the number of stimuli was fixed. Including the ending criterion used by Mishory [5] could have given more interesting results.

The number of simulations is adequate, if not too large. There is no risk of over-fitting, as the data set is not fixed. A large number of different "paths", could, however, be averaged into something having too small a variability. More subjects and thus more TMS sessions would have given results more comparable with the simulation results. A minimum of 10 subjects would have been ideal. In addition, AML method was used only half the number of NML or MN. This is bound to have some effect on the results.

Operators seemed to have trouble with coil orientation and repeating the stimulation exactly at hot spot. Therefore, some of the stimuli which might have caused a proper response at the exact location could have failed. In addition, some of the EMG responses could have been classified falsely, especially if the operator tried to run the method through as fast as possible.

The choice for the target muscle could have some effects as well. There are a lot of nerves controlling the thumb muscle or passing by it. The muscle controlling the little finger (Flexor Digiti Minimi (FDM)) could have been a better choice.

Therefore, a more thorough study should be conducted including all estimation methods in both simulations and navigated TMS study. Furthermore, it should be ensured that the same number of estimates are acquired from the study. Choosing a different muscle and ensuring that the estimation methods are not recognized should prevent the operators rushing and using preliminary knowledge. In addition, the sensibility of the hot spot should be checked. Finally, employing an ending criterion in the maximum likelihood methods should be implemented to find out the true capabilities of the methods.

The results of this study provide further support for the idea that there are little differences between the estimation methods. They provide enough information for choosing an estimation method to be implemented as a computerized tool; although, none of the methods proved to be especially better than the others. The results are collected in Table 7, where the best method for each criterion is marked with the letter 'X'.

Table 7: Matrix for choosing the best method. The best method for each criterion is marked with the letter 'X'.

Criterion	NML	MN	AML
Accuracy	X		-
Precision	X	X	X
Least number of stimuli	X		X
Shortest estimation time			X

However, of these three methods, MN is the only one with a completely defined procedure including the ending point.

8 Conclusions

This thesis discussed the lack of a standard way to estimate MT. An attempt was made to select the best method to implement as a computerized tool out of three candidates. Two of the estimation methods (MN and AML) were presented previously and the third, NML, was a new variant of maximum likelihood method. The study was made using both simulation and navigated TMS.

Two of the previous studies conducted reached a conclusion that AML performs faster, more accurate, and with least stimuli [5, 6]. One study, on the other hand, concluded that there were no significant differences between methods [47]. However, most of these previous studies had modified the estimation methods.

The results from this study coincide with the previous findings in that AML indeed turned out to be the fastest. On the other hand, there were no significant differences between the accuracy and precision of the methods. Although our hypothesis of NML performing better than AML, was falsified it did not perform significantly worse, either. From Table 7 one can see, that choosing either of the maximum likelihood methods is preferred.

Therefore, this study concludes that it does not matter which estimation method is chosen, if one is simply interested in the resulting estimate. However, if the number of stimuli used or the measurement time is of interest, then choosing either of the maximum likelihood methods over MN is recommended.

The structure of the nervous system is unique in all humans. Therefore, the TMS pulse affects each person differently. As MT provides information of the connection between the brain and the target muscle, it is used to determine dosage for the rTMS therapy for several disorders, such as stroke or severe depression. Although, if determination of MT fails, for example, due to a broken nerve path, it does not give any information on where the damage is. There exists a risk of reaching this conclusion if TMS is used falsely - i.e., stimulating the wrong area on the cortex. Therefore, it should always be ensured that the stimulation location is correct. Additionally, repeating the stimulus accurately in that location matters. Navigated TMS provides a solution to this.

There is no doubt that a standard way to estimate MT is needed. However, further studies of the variability of the MT are needed to find out the effect of, for example, thinking of moving the target muscle or watching someone else move it. That is, if the variability is large, it might turn out that MT should be estimated in every treatment session in, for example, stroke therapy.

This study recommends, that a standard estimation method should be chosen such that it is easy to apply in any situation (i.e., with healthy subjects and with patients with severe neurological disorders). It should be included in the treatment procedures (as, for instance, in depression therapy). If implemented as a part of rTMS therapy, the minimizing the number of used pulses seems pointless.

In addition, according to the study of Mishory, a fully automated estimation is

possible. This should reduce the estimation time even further as well as release the operator to fully concentrate on stimulating. Additionally, a fully automated estimation could probably be usable regardless of operator's experience level.

Another concern is the definition of MT as the percentage of stimulator output intensity. As the stimulator designs differ, two stimulators set to 50% probably induce significantly different electric fields on the cortex. Danner et al. have suggested that presenting MT as computed electric field as opposed to PSO results in more comparable values [15].

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